REMARKS

Claims 1-6, 15, 18-20 and 23-26 are pending in the above-identified application, from which Claims 2-4, 19, 25 and 26 are withdrawn from consideration. Claims 1, 5-6, 15, 18, 20, and 23 are rejected as discussed below. Upon entry of the response, Claims 1-6, 15, 18-20 and 23-26 remain pending, Claims 2-4, 19, 25 and 26 remain withdrawn, and Claims 1, 5, 6, 15, 18, 20 and 23 are presented for further examination.

Rejection of Claims Under 35 U.S.C. §103

Claims 1, 5-6, 15, 18, 20 and 23 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Handler *et al.* (1998. *PNAS* 95:7520-7525, hereinafter "Handler") in view of Kim *et al.* (U.S. Patent No. 6,479,626, hereinafter "Kim"), Katz *et al.* (1996. *Virology* 217:178-190, hereinafter "Katz"), Elledge *et al.* (U.S. Patent No. 6,828,093, hereinafter "Elledge") and either Grigliatti *et al.* (U.S. Patent Publication No. 2002/0116723, hereinafter "Grigliatti") or McFarlane *et al.* (1996. *Transgenic Res* 5(3):171-177, hereinafter "McFarlane"). Applicant respectfully disagrees.

Standard for Obviousness

The Patent and Trademark Office has the burden under section 103 to establish a *prima facie* case of obviousness. *In re Piasecki*, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-87 (Fed. Cir. 1984). To establish a *prima facie* case of obviousness, three basic criteria must be met: first, the prior art reference (or references when combined) must teach or suggest all the claim limitations; second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; finally, there must be a reasonable expectation of success. *See* M.P.E.P. §2143.

The Claims

The claims relate to a composition containing a single nucleic acid construct that includes (i) a transgene, flanked by piggyBac transposon-derived terminal repeats, to be integrated into a target host genome for non-transient expression in the host, and (ii) a nucleic acid sequence that encodes a chimeric integrating enzyme that catalyzes integration of the transgene into the target

host genome. The chimeric integrating enzyme, which refers to a genetically engineered recombinant protein wherein the domains thereof are derived from heterologous coding regions, includes a zinc-finger-derived DNA binding domain as well as an enzymatic integrating domain derived from piggyBac transposase. Accordingly, Claim 1 recites a composition comprising a nucleic acid construct comprising: a transgene flanked by two terminal repeat sequences, wherein the terminal repeat sequences are derived from piggyBac transposon; and a nucleic acid sequence encoding a chimeric integrating enzyme under the control of a promoter element, comprising a DNA binding domain and an enzymatic integrating domain, wherein the DNA binding domain is derived from a zinc finger domain and wherein the enzymatic integrating domain is derived from piggyBac transposase. Claims 5-6, 15, 18, 20, 23 and 24 depend from Claim 1 and contain all the features thereof as well as additional features recited in the claims.

The claims are not obvious over the combination of Handler in view of Kim, Katz, Elledge and Grigliatti

Claims 1, 5, 6, 15, 18 and 20 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Handler in view of Kim, Katz, Elledge and Grigliatti. Applicant respectfully disagrees.

The premise of the Examiner's argument appears based on the Examiner's perception that a transposase is interchangeable with a recombinase or an integrase, as evidenced by the Examiner's reliance on the disclosures of Kim, Katz and Elledge. Specifically, the Examiner relies on a single reference in Elledge that incorrectly idenitifies that the term "site-specific recombinase" refers to enzymes that include recombinases, transposases and integrases. At best, Elledge can be said to act as his own lexicographer in defining the term "site-specific recombinase" for the patent application. The Examiner uses this incorrectly defined term to allege that piggyBac transposase is an art-recognized species within a genus of site-specific recombination enzymes comprising transposases, integrases and recombinases. Accordingly, the Examiner combines references directed to either integrases or recombinases (Kim, Katz) with references directed to transposases (Handler, Grigliatti) to set forth a *prima facie* case of obviousness.

However, as evidenced by the Office communication mailed on December 12, 2007 for the instant application, the Patent Office recognized that transposases are a patentably distinct

species from integrases and recombinases. It was acknowledged that these species are not obvious variants of each other and do not relate to a single general inventive concept because they lack the same or corresponding special technical features. A portion of the Office communication is reproduced below for the Examiner's convenience:

> "Prior to the invention, the art had long-recognized that each integrating enzyme possess its own special technical feature because each enzyme recognizes a distinctly different nucleic acid sequence, thereby generating site-specificity for integration and/or exeision of the nucleic acid.
>
> ...
>
> There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph."

In addition to the Office's recognition of the distinction between transposases, integrases and recombinases, Applicant respectfully submits that a person of ordinary skill in the art would consider transposases, recombinases and integrases to be distinctly different in both evolutionary and mechanistic terms. *See*, for example, Coates *et al.* (2005. *Trends in Biotechnology* 23(8):407-419), which is submitted herewith. For example, integrases only allow for the insertion of a nucleic acid sequence into another sequence; however, integrases cannot catalyze excision of the same nucleic acid sequence out of a longer sequence within which it may be located. Recombinases (classified as general or site-specific) catalyze a process in which a first and a second nucleic acid molecule having identical or substantially similar sequences (*i.e.* are "homologous), or having nucleic acid segments that possess a limited degree of sequence homology, are cut and recombined such that a first region of the first molecule becomes ligated to a second region of the second molecule while the corresponding first region of the second molecule becomes ligated to the corresponding second region of the first molecule. In contrast, transposases catalyze the movement of nucleic acid segments out of one sequence and into another sequence by a specific "cut" and then "paste" mechanism. These enzymes are

distinguished from recombinases and integrases by incorporating both distinct excisional and/or integrating capabilities. Furthermore, transposases have sequence specificity with regard to their transposon ends but, unlike recombinases, recognize a loose or short consensus sequence for site integration. For example, piggyBac transposase uniquely recognizes a short TTAA nucleotide sequence.Accordingly, Applicant respectfully submits what the Office has already aeknowledged, namely, that the art recognizes that a transposase is distinct from an integrase or a recombinase.

Thus, when the references are properly considered for what they actually disclose, the present rejection fails to make a *prima facie* case of obviousness. The combination of references is based on a premise that is not accepted by the scientific community and which contradicts the Office's own position on the distinction between transposases, recombinases and integrases. Accordingly, not only would there be no motivation to combine the references, which are drawn to distinct types of integrating enzymes, but the combination of references also does not teach all the elements of the claimed subject matter.

Handler teaches germ-line transformation of a medfly *w* host strain using two separate vectors: a first vector encoding a transgene (the medfly *w* gene) and a second vector encoding the normally regulated piggyBac transposase. However, as acknowledged in the Office Action, Handler does not teach or suggest that piggyBac transposase is part of a chimeric integrating enzyme. In addition, Handler does not teach or suggest that the transgene and transposase are on a single nucleic acid construct.

Kim is relied upon for teaching that DNA binding domains include zinc finger proteins and helix-loop-helix motifs. Kim teaches design strategies for. providing flexible linkers that fuse two DNA binding domains of a "chimeric zinc finger protein," which is composed of two or more DNA-binding domains, one of which is a zinc finger polypeptide, wherein the two domains can be the same or heterologous. In some embodiments, the chimeric zinc finger can further include a regulatory domain polypeptide, such as, for example, an integrase or a recombinase. However, Kim is silent with respect to transposases, which the Office and the art recognize as distinct from recombinases and integrases. Thus, Kim does not teach or suggest a chimeric integrating enzyme comprising a zinc finger-derived DNA binding domain and a transposase-derived integrating domain, let alone a piggyBac transposase integrating domain. In addition,

the reference does not teach or suggest a transgene and the chimeric integrating enzyme in a single nucleic acid construct.

Katz is relied upon for teaching a chimeric integrating enzyme that contains the DNA-binding domain of LexA repressor protein fused to the catalytic domain of avian sarcoma virus (ASV) integrase enzyme, wherein the DNA-binding domain of LexA is present at the N-terminus of the fusion protein. In constructing the ASV integrase-LexA repressor DNA-binding domain fusion construct, the authors removed all or a part of the ASV integrase zinc-finger domain. Thus, the chimeric integrating enzyme of Katz lacks a functional zinc-finger binding domain. In contrast, the chimeric integrating enzyme of the claimed subject matter includes a zinc-finger-derived DNA binding domain. Furthermore, Katz teaches that the chimeric integrating enzyme includes the ASV integrase catalytic domain. However, Katz is silent with respect to transposases, which the Office and the art recognize as being distinct from integrases. Thus, Katz does not teach or suggest the chimeric integrating enzyme, which includes a piggyBac transposase-derived integrating enzyme, of the claims. In addition, the reference is silent with respect to a transgene and the recited chimeric integrating enzyme being located on a single nucleic acid construct.

Elledge is relied upon for allegedly teaching that, at the time of the invention, piggyBac transposase was an art-recognized species within the genus of site-specific recombination enzymes comprising transposases, integrases and recombinases. However, the Examiner is relying on a single reference in Elledge where the reference indicates that the term "site-specific recombinase" refers to enzymes that include recombinases, transposases, and integrases. Notwithstanding the fact that many integrases are not site-specific, this statement also incorrectly classifies transposases as a recombinase and is not in agreement with what the scientific community or the Office recognize about transposases, recombinases and integrases. As recognized by those of skill in the art, a site-specific recombinase does **not** refer to any enzyme that is a recombinase, a transposase or an integrase but instead refers to a tyrosine recombinase (in which DNA is covalently attached to a tyrosine residue) or to a serine recombinase (in which DNA is covalently attached to a serine residue). Such site-specific recombinases catalyze DNA strand exchange between DNA segments by binding to specific recognition sites that are usually between about 30 and 200 nucleotides in length, cleaving the DNA backbone, exchanging the

strands of a first and a second DNA double helix, and religating the DNA. This is distinct from the mechansim and action of a transposase. Furthermore, the disclosure of Elledge is specifically directed to vectors containing the Cre-loxP recombinase system. The reference does not teach or suggest piggyBac transposase, a chimeric integrating enzyme containing a zinc finger-derived DNA binding domain and a piggyBac transposase-derived integrating domain, or a transgene and the recited chimeric integrating enzyme on a single nucleic acid construct.

Grigliatti is relied upon for allegedly teaching transposon-based transformation vectors comprising the use of piggyBac transposase, wherein the transposon vector comprises terminal repeats, and wherein the transposase gene and heterologous protein expression cassette are within the transposon terminii. In particular, the Examiner notes that "Applicant appears to have overlooked that the nucleic acid construct of Grigliatti et al ('723) comprising *(sic)* i) an inducible promoter operably linked to a transposase, and ii) a transgene expressing a heterologous protein [0026]." However, the disclosure of Grigliatti is specifically directed to vectors containing the **P element** transposase for use in insect cells. The P element transposase is distinct from piggyBac transposase and, unlike piggyBac transposase, requires insect host cell factors to operate. Furthermore, unlike piggyBac transposase, the P element transposase does not recognize a TTAA nucleotide sequence, which is required for transgene integration catalyzed by piggyBac transposase. The only reference to piggyBac transposase is a general statement in Grigliatti regarding the creation of inducible transposase producing cell lines. However, the reference does not teach or suggest piggyBac transposase in a single nucleic acid construct with a transgene, nor does the reference teach or suggest a chimeric integrating enzyme that contains a zinc finger-derived DNA binding domain and a piggyBac transposase-derived integrating domain.

The premise of the Office Action's reliance upon Kim, Katz and Elledge is the notion that transposases, recombinases and integrases are obvious variants and interchangeable. Given that the reliance of the Office Action is based upon a premise that is not accepted by the scientific community nor by the Office itself as discussed in great detail *supra*, any rejection that is based upon this premise (and upon Kim, Katz and Elledge) cannot be maintained. Since the basis for the combination of references is without merit, there would be no motivation to

combine the references, which are directed to distinct types of integrating enzymes. In addition, the combination of references does not teach all the features of the claims.

Thus, in view of the foregoing, Applicant respectfully submits that the claims are not obvious over the cited combination of references. Withdrawal of the rejection under this section is respectfully requested.

Claim 23 is not obvious over the combination of Handler in view of Kim, Katz, Elledge and McFarlane

The rejection of Claim 23 under 35 U.S.C. §103(a) as allegedly being unpatentable over Handler in view of the Kim, Katz, and Elledge, as applied to Claims 1, 5-6, 15, 18 and 20, and further in view of McFarlane *et al.* (1996. *Transgenic Res.* 5(3):171-177; Abstract only, hereinafter "McFarlane") is maintained. McFarlane is relied upon for teaching the inclusion of a nucleic acid sequence having 5 base pairs that were homologous to the host DNA. Applicant respectfully disagrees.

The deficiencies of Handler, Kim, Katz and Elledge as applied to Claims 1, 5-6, 15, 18 and 20 are discussed above. McFarlane does not repair the deficiencies of the combination of references because the reference does not teach or suggest a chimeric integrating enzyme that includes is a zinc finger-derived DNA binding domain and a piggyBac transposase-derived integrating domain. In addition, McFarlane does not teach or suggest a transgene and the recited chimeric integrating enzyme in a single nucleic acid construct. Accordingly, the cited combination of Handler, Kim, Katz, Elledge and McFarlane does not teach or suggest all the elements of the claims.

In view of the foregoing, Applicant respectfully submits that Claim 23 is patentable over the cited combination of references, and withdrawal of the rejection under 35 U.S.C. §103 is requested.

Conclusion

Applicants submit that the present Application is in condition for allowance and respectfully request the same. If any issues remain, the Examiner is cordially invited to contact Applicants' representative at the number provided below in order to resolve such issues promptly.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 04-0258.

Respectfully submitted,

Dated: April 20, 2009 By: 

Karen W. Lai
Registration No. 60,920
Agent of Record
DAVIS WRIGHT TREMAINE LLP
505 Montgomery Street, Suite 800
San Francisco, California 94111-3611
(415) 276-6500